library of exogenous scaffolds;

b) introducing into said plurality of cells a library of nucleic acids each encoding at least a first enzyme and a second enzyme, wherein each of said enzymes comprises an exogenous binding sequence; and

c) screening said plurality of cells for a cell comprising at least one exogenous scaffold and exhibiting an altered phenotype,

wherein each of said scaffolds comprises at least a first binding site and a second binding site, and wherein said first enzyme binds to said first binding site and said second enzyme binds to said second binding site.

REMARKS

Claims 58-80 are pending in the application. Claim 58 has been amended to recite that the enzymes comprise exogenous binding sequences. Support is found in the specification on page 4, lines 6-10 and page 8, lines 13-20. No new matter is entered by way of the amendments.

Attached hereto is a marked up version captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE" showing changes made to the claim by the amendments. In addition, an Appendix of the Pending Claims is attached for the Examiner's convenience.

Favorable consideration of the following comments as they may apply to the outstanding rejections is respectfully requested for the reasons that follow.

Finality of the Office Action

As a preliminary matter, Applicants respectfully request reconsideration of the finality of the Office Action. First, the Examiner has submitted the reference of Pikus et al. Biochemistry 35: 9106-9119 (1996) ("Pikus") as extrinsic evidence to support the inherency of scaffolds. This new reference was neither necessitated by Applicants' amendment of the claims nor based on any references in a informational disclosure statement. The reference is neither subsidiary nor cumulative since it is directed towards answering Applicants' arguments concerning the structure of the enzymes cited in the prior art references. As Pikus is a newly cited art used to support rejections of non-amended claims, Applicants submit that the final rejection is premature. See M.P.E.P. § 706.07(a)

Second, the prior Office Action (Paper No. 28) provided only the first few pages of

Srere, P.A, Ann. Rev. Biochem. 56: 89-124 (1987), a review article proffered as extrinsic evidence to support the inherency of scaffolds in Minshull et al. (U.S. Patent No. 5,837,458). As provided in 37 C.F.R. § 1.104 regarding Examiner Actions

> The reasons for any adverse action or any objection or requirement will be stated in an Office Action and such information or references will be given as may be useful in aiding the applicant . . . .

Since the substance of the information in Srere was not properly provided as required, Applicants were not given a full and fair opportunity to respond to the merits of the prior Office Action. In view of these circumstances, the final rejection for this case appears improper.

Third, the current Office Action adds another basis of rejection under 35 U.S.C. § 112, first paragraph for lack of enablement. As further discussed below, the prior Office Action (Paper No. 28) rejected the claims under 35 U.S.C. § 101 and § 112, first paragraph for lack of patentable utility and did not reject the claims based on § 112, first paragraph for lack of enablement. It is Applicants understanding that utility and enablement are two separate requirements for patentability. Since a final rejection should not be given if a new basis of rejection is used, the finality of the Office Action should not have been issued in this case. See M.P.E.P 706.07(a).

Given all of the above, Applicants respectfully request withdrawal of the finality of the Office Action. Should the Examiner concur on this point, a refund of the Request for Continued Examination is respectfully requested.

Rejections Under 35 U.S.C. § 101

Claims 58-80 are rejected under 35 U.S.C. § 101 for lack of patentable utility. The Examiner appears to conclude that the claimed methods are not supported by a specific and substantial utility or a well established utility because the screening method "does not result in a product with specific and substantial utility" and therefore lacks description of a specific benefit to the public. Applicants respectfully traverse.

The M.P.E.P. at § 2107.01 sets forth the guidelines for determining patentable utility. As the Examiner is well aware, there must be a credible assertion of a specific and substantial utility or a well established utility to satisfy the utility requirement. For determining specific utility, the guidelines state

> Office personnel should distinguish between situations *where an applicant has disclosed a specific use or application of the invention* and situations where an applicant merely indicates that the invention may prove useful without identifying with specificity why it is considered useful.

See M.P.E.P. § 2107.01(I). Several examples are given describing practical application of this requirement:

> For example, indicating that a compound may be useful in treating *unspecified disorders*, or that the compound has "useful biological" properties, would not be sufficient to define a specific utility. Similarly, a claim to a polynucleotide whose use is disclosed simply as a gene probe or chromosomal marker would not be considered to be specific in the absence of a disclosure of a specific DNA target. A general statement of diagnostic utility, such as *diagnosing an unspecified disease*, would ordinarily be insufficient absent a disclosure of what condition is being diagnosed.

See id. (emphasis added). Substantial utility is whether there is "real world' context use for the claimed invention. Examples for determining substantial utility are also given:

> an *assay method for identifying compounds that themselves have substantial utility define a real world context of use*. . . . Many research tools such as gas chromatography, *screening assays*, and sequencing techniques have a clear, specific and unquestionable utility.

See id. Several illustrative examples that do not meet the substantial utility requirement include the following:

> (B) A method of treating an *unspecified disease*;
> (C) A method of assaying for or *identifying a material that itself has no specific and/or substantial utility*.

See id. Thus the standard for substantial utility is "any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient." See id.

In view of the above, Applicants direct the Examiner to passages in the specification describing various specific and substantial utilities and well established utility for the claimed methods. The specification on page 42 provides

> the growth and/or spread of certain tumor types is enhanced by stimulatory responses from growth factors and cytokines (PDGF, EGF, Heregulin, and others) which bind to receptors on the cell surfaces of specific tumors. In a preferred embodiment, the methods of the invention are used to inhibit or stop tumor growth and/or spread, by finding *bioactive agents capable of blocking the ability of the growth factor or cytokine to stimulate the tumor cells*. The introduction of

> libraries of enzyme complexes into specific tumor cells with the addition of growth factor or cytokine, followed by selection of bioactive agents which block the binding, signaling , phenotypic and/or function responses of these tumor cells to the growth factors or cytokine in question.

It is well known that growth factors EGF and Heregulin are involved in genesis of specific tumors types, including malignant breast cancer and ovarian cancer. The disclosure makes reference to a specified disorder (i.e., tumors) controlled by specific biological agents (e.g., EGF and Heregulin). The specification states that the claimed methods are useful for identifying biological agents that inhibit the activity of these growth factors, thereby inhibiting or slowing tumor cell growth. As such, the specification provides an assertion of specific utility in the context of a specified disorder affected by a specific biological agent. Substantial utility is given in that the methods allow assaying for compounds that inhibit the effect of growth factors on tumor cell growth, thereby providing a specific benefit to the public. Another illustration of utility is given on page 50, lines 21-29, which states

> One example of many is the ability to block *HIV infections*. HIV requires CD4 and a co-receptor which can be one of several seven transmembrance G-protein coupled receptors. In the case of infection of macrophages, CCR-5 is the required co-receptor, and there is strong evidence that a block on CCR-5 will result in resistance to HIV-1 infection. There are two lines of evidence for this statement. First it is known that the natural ligands for CCR-5, the CC chemokines RANTES, MIP1a and MIP1b are responsible for CD8+ mediated resistance to HIV. Second, individuals homozygous for a mutant allele of CCR-5 are completely resistant to HIV infection. Thus an inhibitor of the CCR-5/HIV interaction would be of enormous interest to both biologists and clinicians.

(emphasis added). As with the embodiment discussed above, this paragraph provides an assertion of specific utility, namely assaying for agents that block interaction of CCR-5 and HIV virus, the known etiological agent responsible for acquired immune deficiency syndrome (AIDS). There is substantial utility - real world benefit - in that identifying agents that block HIV interaction with its receptor would have public benefit in reducing HIV infectivity. In these given examples, Applicants have disclosed application to specific diseases and described a public benefit for the claimed method that complies with the specific and substantial utility requirement.

In further support, Applicants direct the Examiner to the specification on page 51, lines 22-29, which describes the following:

> Antibiotic drugs that are widely used have certain dose dependent, tissue specific toxicities. For example renal toxicity is seen with the use of *gentamicin*,

> *tobramycin*, and *amphotericin*; hepatotoxicity is seen with the use of INH and *rifampin*; bone marrow toxicity is seen with *choramphenicol*; platelet toxicity is seen with *ticarcillin*, etc. These toxicities limit their use. Enzyme complexes can be introduced into the specific cell types where specific changes leading to cellular damage or apoptosis by the antibiotics are produced, and bioactive agents can be isolated that confer protection, when these cells are treated with these specific antibiotics.

Additional descriptions of drug toxicity problems are provided in the following the passage:

> In a preferred embodiment, the present methods are useful in drug toxicities and drug resistance applications. Drug toxicity is a significant clinical problem. This may manifest itself as specific tissue or cell damage with the result that the effectiveness is limited. Examples include myeloablation in high dose cancer chemotherapy, damage to epithelial cells lining the airway and gut, and hair loss. Specific examples include *adriamycin* induced cardiomyocyte death, *cisplatinin*-induced kidney toxicity, *vincristine*-induced gut motility disorders, and *cyclosporin* induced kidney damage. Enzyme complexes can be introduced into specific cell types with characteristic drug-induced phenotypic or functional responses, in the presence of the drugs, and agents isolated which reverse or protect the specific cell type against toxic changes when exposed to the drug.

(page 52, lines 10-20) (emphasis added). The description gives a specific utility, which is altering a tissue or cell tolerance to specific toxic drugs, such as gentamicin, tobramycin, amphotericin, adriamycin, cisplatinin, vincristine, and cyclosporin, which are used routinely used in clinical settings. Substantial utility is also met since a screen for enzyme combinations that decrease drug toxicity by drug biotransformation or altering cell biological mechanisms provides a specific benefit to patients who react adversely to such drug therapy. In keeping with Examiner's polyketide example, Applicants have described specific compounds whose transformation, directly or indirectly, results in a specific benefit to the public.

In view of the foregoing, Applicants submit that the claimed methods satisfy the utility requirement under 35 U.S.C. §101. Accordingly, withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, first paragraph: enablement

Claims 58-80 are rejected under 35 U.S.C. § 112, first paragraph for lack of an enabling disclosure. Applicants respectfully traverse.

As a matter of clarification, the prior Office Action (Paper No. 28) rejected the claims under § 112, first paragraph for lack of patentable utility. The following is quoted from page 3 of the prior Office Action:

> The assertion in the specification cited above *does not satisfy the utility requirement of 35 U.S.C. 101 and 112(1)* for the following reasons.

(emphasis added). The prior Office Action also states on page 5

> Claims 58-79 are also rejected under 35 U.S.C. 112 first paragraph. Specifically, since the *claimed invention is not supported by either a specific asserted utility or a well established utility* for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(emphasis added). The relationship and form for a § 101/112, first paragraph rejection based on utility are given in M.P.E.P. § 2107.01(IV), which reads in part

> [t]o avoid confusion, any rejection that is imposed on the basis of 35 U.S.C. 101 should be accompanied by a rejection based on 112, first paragraph. The 35 U.S.C. 112, first paragraph should be set out as a separate rejection that incorporates by the reference the factual basis and conclusion set forth in the 35 U.S.C. 101 rejection. The 35 U.S.C. 112, first paragraph rejection should indicate that because the claimed invention as claimed does not have utility, a person skilled in the art would not be able to use the invention as claimed . . . *To avoid confusion during examination, any rejection based on grounds "other than lack of utility" should be imposed separately from any rejection imposed due to lack of utility under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph.*

(emphasis added). In the previous Office Action, no rejections were given based on § 112, first paragraph for lack of enablement. In the present Office Action, however, the Examiner has asserted in a separate heading a 35 U.S.C. § 112, first paragraph rejection for lack of enablement, thus advancing a new basis for rejection of the claims. As provided in M.P.E.P. § 706.07(a), a final rejection should not be made "where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement . . . ." Consequently, Applicants respectfully submit that imposing a final rejection in the present Office Action is improper. Accordingly, Applicants respectfully request withdrawal of the finality of the Office Action and clarification of the basis of the rejections.

For the present circumstances, Applicants address the rejection as one based on lack

of enablement. The Office Action advances a number of reasons for insufficiency of the disclosure under § 112, first paragraph, including (1) insufficient guidance in the specification for a person skilled in the art to correlate libraries, scaffolds, phenotypic changes, and assay methods; (2) absence of working examples; (3) unpredictability in the art for screening for phenotypic changes caused by a combination of exogenous scaffold with a library of nucleic acids encoding enzymes; and (3) the level of experimentation required to determine what library would work with a particular scaffold to produce a phenotypic change in a cell that is not caused by the library alone. Based on the above, the Examiner concludes that undue experimentation is required to practice the claimed screening methods. Applicants respectfully traverse.

The standard for sufficiency of enablement is not whether experimentation is necessary to practice the claimed invention but whether experimentation is undue. See M.P.E.P. § 2164.01. A considerable amount of experimentation is permissible, even if complex, "if the art typically engages in such experimentation or if the specification provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed." See In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988); see also M.P.E.P. § 2164.01.

The factors to consider in determining whether experimentation is undue include (a) breath of the claims; (b) nature of the invention; (c) state of the prior art; (d) relative skill of those in the art; (e) predictability or unpredictability of the art; (f) amount of direction in the specification; (g) presence or absence of working examples; and (h) quantity of experimentation required in order to practice the invention. See In re Wands at 1404. An assessment of enablement cannot be based on only one of the factors while ignoring one or more of the others. See id. In view of these criterias, Applicants submit that the experimentation required to practice the claimed screening methods is not undue.

Regarding the breath of the claims, nature of the invention, and state of the prior art, the claims recite elements and procedures that are already known in the art. Numerous screening methods are known. For instance, a perusal of Minshull shows descriptions of various types of screening assays including, among others, screens for products acted on by metabolic enzymatic pathways, screens for assessing drug resistance/sensitivity mechanisms, screens for markers of gene expression, screens for differentially expressed proteins, screens for enzyme inhibitor assays, protein expression screens using antibodies, and screens for

production of compounds that stimulate growth of reporter cells. Moreover, methods for making and using chimeric proteins with binding sequences are conventional in the art. Applicants invite the Examiner's attention to Exhibit A: Ruden et al., "*Generating yeast transcriptional activators containing no yeast protein sequences*," Nature 350: 250-252 (1991). This article describes random *E.coli.* peptides fused to the DNA binding sequences of LexA or GAL4 transcription factors to direct the peptides to DNA binding sites on cellular promoter-reporter constructs. A person skilled in the art would have readily extrapolated these and others, including various known protein-protein interaction domains, to the claimed method given the guidance in the specification. In view of the state of the prior art and the nature of the claims, the disclosure enables the full scope of the claims.

Regarding the relative skill of the art, the technical knowledge and skill in the biological and biotechnological arts is highly advanced. It is routine practice to synthesize nucleic acid libraries, generate stable cells lines containing exogenous nucleic acids, express nucleic acids and proteins within cells, and screen for altered phenotypes. The reference of Minshull is confirmation of this high skill in the art.

Regarding predictability or unpredictability in the art, the "predictability or lack thereof" in the art refers to "the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention." See M.P.E.P. § 2100-178. Given the advanced knowledge in the biological arts, it would not take undue experimentation to extrapolate what is known to the claimed screening methods. In addition, the guidelines provide that

> it is incumbent upon the Patent Office, whenever a rejection on this basis [enablement] is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is consistent with the contested statement.

See M.P.E.P 2164.04. In this case, a generalized statement of unpredictability is asserted without providing objective evidence or reasoning, other than a recitation of the claim language, to support the conclusion.

Regarding the absence of working examples, the M.P.E.P. at § 2164.04 provides that reduction to practice is not a requirement for enablement. Thus the specification need not have working examples if a person skilled in the art is able to practice the invention without undue experimentation. Given the knowledge in the art and the direction given in the disclosure, Applicants submit that a skilled artisan can practice the claimed invention without

undue experimentation.

Regarding the amount of direction and guidance given in the disclosure, there is sufficient guidance and direction for a skilled artisan to practice the claimed screening method. The specification provides sufficient descriptions of scaffolds, binding sites, binding sequences, enzymes, and screening methods for a ordinary person skilled in the art to practice the screening methods. The claims and the specification amply correlates the scaffolds, enzymes, and altered phenotypes to be screened. For example, interrelationships of the scaffolds and enzymes bound to scaffolds for producing novel enzymatic pathways and altered phenotypes are described throughout the specification, particularly on pages 5 and 33. The relationship of scaffolds, binding sites, and binding sequences are given on page 7-8. Altered phenotypes due to the enzymes and exogenous bioactive agents are described on page 36-37, with specific embodiments given on pages 42-56. Accordingly, the disclosure provides ample guidance and direction for a skilled artisan to practice the claimed methods.

Regarding the quantity of experiment necessary to practice the screening method, applicants reiterate the guidelines provided in M.P.E.P. § 2164.06:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed.

For example, determining whether an altered phenotype is due to a scaffold, enzymes, or enzymes bound to scaffolds are routine control experiments carried out in the screening art. A typical screen would involve examining phenotype of cells containing only exogenous scaffold, examining phenotype of cells containing only enzymes with its requisite binding sequences, and examining phenotype of cells containing both scaffold and enzymes. The scaffold and the enzymes can be isolated from a cell displaying an altered phenotype and reintroduced into same background cell not containing these elements to verify the effect.

In view of the high level of skill in the art and the guidance and direction given in the specification, the level of experimentation required to practice the claimed method is not undue. This conclusion is well supported because, as manifested in Minshull, the art typically carries out complicated screening methods.

For the reasons above, Applicants submit that the claimed screening methods are enabled. Accordingly, withdrawal of the rejection under 35 U.S.C. § 112, first paragraph of

claims 58-80 is respectfully requested.

Rejections Under 35 U.S.C. § 112, first paragraph: written description

Claims 58-80 stand rejected under 35 U.S.C. § 112, first paragraph for lack of sufficient written description. The Examiner contends that the specification does not adequately provide a written description of the materials needed to perform the screens commensurate with the scope of the claims and that representative examples of using the claimed method have not been provided. Applicants respectfully traverse.

The cases cited by the Examiner, particularly University of California v. Eli Lilly, 43 USPQ2d 1398 (Fed. Cir. 1997), does not properly address the issue of process claims. The issue in University of California involved claims directed to cDNAs encoding vertebrate insulin where the disclosure provided the sequence of only a rat insulin cDNA sequence. The court held that a description of a single species of cDNA did not adequately describe the claimed genus of vertebrate insulin cDNAs. The Federal Circuit concluded that to satisfy the written description in such instances (i.e., claims to compositions) required disclosure of a number of species representative of the genus. The USPTO following the decision in University of California v. Eli Lilly issued the "Interim Guidelines for the Examination of Patent Applications Under 35 U.S.C. 112, ¶ 1 Written Description Requirement" requiring the disclosure of a representative number of species with relevant identifying characteristics for satisfying written description in similar situations. The guidelines, however, further stated

> These Interim Guidelines are directed primarily to determining whether there is written description support for product claims and are not intended to specifically address the description necessary to support process or product by process claims.

See Federal Register Vol 63, No. 114, July 15 1998, 32639. With due respect, requiring representative examples of using the claimed method appears to be an inappropriate application of the written description requirement enunciated in University of California v. Eli Lilly.

A more cogent guide for assessing written description for process claims is provided in the USPTO's "Revised Interim Written Description Guidelines Training Materials" (available at http://www.uspto.gov/web/patents/guides.htm). Applicants direct the Examiner to "Written Description Original Claims -- Decision Tree--" on pages 8 and 9 and the case

study, Example 12, on page 47-49. In the hypothetical case and the accompanying explanatory notes, it states that a specification need not disclose the details of a particular step and not even disclose actual reduction to practice of the claims to satisfy the written description requirement if the specification read in light of the knowledge and level of skill in the art discloses the complete steps of the claimed process. Thus, an inventor need not disclose every detail of his invention "if one skilled in the art would understand what is intended and know how to carry it out." It is further stated in M.P.E.P. § 2163(II)(A)(3)(a)

> the description need only describe in detail that which is new or not conventional. . . . If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.

As applicants have discussed above, protein-protein and protein-nucleic acid interaction domains are well known in the art. Chimeric proteins containing binding sequences that interact with binding sites are routinely made and introduced into cells. Numerous enzymes and nucleic acids encoding them have been cloned and sequenced. A variety of screening assays are described in the specification. Moreover, as noted herein, the art typically engages in screening cells for altered phenotypes.

Given this knowledge of what is conventional in the art, the specification has sufficiently disclosed the complete steps of the claimed process. The specification clearly identifies the distinguishing steps of the claimed method with all its limitations to show that applicants were in possession of the claimed invention, thus sufficiently complying with the written description requirement. Accordingly, withdrawal of the rejections under 35 U.S.C. § 112, first paragraph for claims 58-80 is respectfully requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 58-80 are rejected under 35 U.S.C. § 112, for omitting essential steps in screening a plurality of cells. Applicant respectfully traverse.

The step of "screening said plurality of cells" further includes the phrase "for a cell comprising at least one exogenous scaffold and exhibiting an altered phenotype." When properly viewed in its entirety, the claim delineates the screening step as comprising identifying cells comprising at least one exogenous scaffold and exhibiting an altered phenotype. As noted in Applicants' prior response, screens for altered phenotypes are given

on page 36 and 37, with specific embodiments given throughout the specification. Thus, the claims read in light of the specification sufficiently define the necessary attributes of the screening process.

Applicants also refer to the prior art reference of Minshull as a useful reference point for assessing definiteness in this case. Representative independent claim 1 recites in step b)

> screening the library to identify at least one recombinant gene from the library that confers enhanced ability to catalyze the reaction of interest by the cell relative to a wildtype form of the gene.

This step in the claimed method is similar in form and content to the screening step recited in the present application. The Patent Office found the claims in Minshull sufficiently definite such that it did not require enumeration of specific steps involved in screening of the library. Applicants further point out that a person of ordinary skill in the art reading the claims of the present application is presumed to have knowledge of all the prior art and its contents, including that of Minshull, and therefore would understand the scope of screening a plurality of cells in the instant claims.

Further support is found in a number of Federal Circuit decisions affirming the definiteness of claim terms in similar situations. See In re Warmerdam, 31 USPQ2d 1759 (Fed. Cir. 1994); see also Orthokinetics, Inc. v. Safety Travel Chairs, Inc. 1 USPQ2d 1081 (Fed. Cir. 1986). For instance, a claim at issue in Warmerdam dealt with the following dependent claim:

> 5. A machine having a memory which contains data representing a bubble hierarchy generated by the method of any of claims 1 through 4.

The Board of Patent Appeals rejected the claim as being indefinite for not specifying how the memory is made or produced to contain the bubble hierarchy system. The disclosure lacked description of any computer programs incorporating the claimed algorithms into any type of machine. The Federal Circuit, however, reversed the rejection stating that the dependent claim "plainly covers" all machines with memory programmed to contain data representing the bubble hierarchy because "the methods encompassed by the claims lend themselves to manipulation through known computer technology." See In re Warmerdam, 31 USPQ2d at 1760. Similarly, a person skilled in the art, for example a person studying cell cycle or metabolic enzymes would have no difficulty in understanding what is meant by screening for cells with an "altered phenotype" relevant to their focus of study (e.g., cell cycle, drug

biotransformations, etc.).

Applicants submit that the phrase "screening a plurality of cells for a cell comprising at least one exogenous scaffold and exhibiting an altered phenotype" is delineated with sufficient clarity and precision to satisfy 35 U.S.C. § 112, second paragraph. Accordingly, Applicants respectfully request withdrawal of the rejections.

Claim 58 stands rejected for being indefinite in regards to the term "exogenous scaffolds." Specifically, the Examiner finds that the scope of the term is not sufficiently defined in the specification.

As provided in M.P.E.P. § 2173.02, the definiteness of claim language is determined in view of

> (A) The content of the particular disclosure;
> (B) The teachings of the prior art; and
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the art at the time the invention was made.

Thus, it is encumbent on the Examiner to analyze the claim terms from the point of one skilled in the art. It is well known that the extent of binding sequences and binding sites are dependent on the nature of the interacting species. For example, a DNA binding protein with a DNA binding domain will bind to a nucleic acid of a particular sequence and length, which will differ depending on the particular DNA binding domain. This is well illustrated by the LexA and GAL4 systems discussed above (see Exhibit A). Similarly, the extent of amino acid sequences involved in protein-protein interactions will depend on the nature of the protein-protein interaction domains, many of which were also known at the filing of the instant application. The specification on page 13, lines 20-27 also describes the required degree of specificity between binding sequence and binding site.

A person skilled in the art would have clearly understood the scope of the binding sites on an exogenous scaffold and binding sequences that interact with its cognate binding partner given the state of knowledge and the descriptions in the specification. Since the claims recite that the binding sequences on the enzymes are exogenous binding sequences and that the scaffolds containing the binding site are exogenous scaffolds, a person skilled in the art would select art recognized binding sequence/binding site pairs of sufficient affinity in constructing the enzymes and scaffolds. As provided in the disclosure, the scaffold may also contain connection sites to separate binding sites when the scaffold comprises multiple

binding sites. Given the nature of binding sites and connecting sites useful in constructing the scaffolds, the scope of "exogenous scaffolds" given in the specification and viewed from the perspective of the skilled artisan is as precise as the subject matter permits. Accordingly, withdrawal of the rejection of the rejection is respectfully requested.

Claim 59 stands rejected as being indefinite in regards to the phrase "exogenous bioactive agent precursors." Applicants respectfully traverse.

Claim 59 depends from claim 58, which includes the limitation of "screening a plurality of cells for a cell comprising at one least one exogenous scaffold and exhibiting an *altered phenotype*." (emphasis added). Thus, the screen is for an altered phenotype rather than a screen of cells prior and a screen of cells after addition of exogenous bioactive agent precursor. In other words, the cells are screened for a different phenotype (i.e., altered phenotype) relative to the *phenotype displayed* prior to introduction of enzymes and exogenous bioactive agent. Applicants submit that the phrase is clear to those skilled in the art. Accordingly, withdrawal of the rejection of claim 59 is respectfully requested.

Claim 65 is rejected for being indefinite in regards to the term "targeting sequence." Applicants respectfully traverse.

It is a tenet of patent law that "applicants are their own lexicographers". See M.P.E.P 2173.01. Moreover, the Examiner is required to give the broadest reasonable interpretation consistent with the specification when interpreting the claims. See M.P.E.P. § 2173.05. In the present case, the specification provides a specific description of a targeting sequence on page 16, lines 20-21, which recites

> targeting sequence, defined below, which allow the localization of the scaffolds and enzymes into a subcellular or extracellular compartment.

The specification then defines with particularity the scope of targeting sequences:

> suitable targeting sequences include, but are not limited to, binding sequences capable of causing binding of the expression product to a predetermined molecule or class of molecules while retaining bioactivity of the expression product, (for example by using enzyme inhibitors or substrate sequences to a target a class of relevant enzymes); sequences signaling selective degradation, of itself or co-bound proteins; and signal sequences capable of constitutively localizing the candidate expression products to a predetermined cellular locale, including a) subcellular locations such as Golgi, endoplasmic recticulum, nucleus, nucleoli, nuclear membrane, mitochondria, chloroplast, secretory vesicles, lysosome, and cellular membrane; and b) extracelluar locations via either membrane

anchoring sequences or secretory signal sequences.

Representative examples are disclosed, including specific peptide sequences. Targeting and localization are the effects of a mechanistic process that includes the phenomena of molecular recognition, namely binding interactions. Any overlap or inclusiveness in function or mechanism does not render the terms indefinite since a person skilled in the art would understand that targeting sequences functioning through binding interactions can also serve separately and distinctly as binding sequences on enzymes or binding sites on scaffolds.

In further support, Applicants respectfully draw Examiner's attention to the decision of In re Kelley, 134 USPQ 397 (CCPA 1962) (see also M.P.E.P. § 2173.05(o)). The court stated

> [w]e see no reason why a single structural element . . . which performs two separate functions, cannot support a claim broadly reciting these separate functions.

See In re Kelley at 401. The court concluded that such use did not warrant a finding of indefiniteness since the recited structure did in fact perform two distinct and separate functions in the claims, and therefore presented a reasonable interpretation of the terms under the circumstances. Similarly, targeting sequences can function separately and distinctly from a binding sequence on an enzyme or a binding site on a scaffold. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 66 stands rejected as being indefinite in regards to the term "rescue sequence" because a person skilled in the art would not know what distinguishes rescue sequence from another sequence. Applicants respectfully traverse.

The specification states expressly that a rescue sequence is "a sequence which may be used to purifiy or isolate either the scaffolds, enzymes, or enzyme complex, or the nucleic acids encoding them." (Page 22, lines12-14). It is well known in the art that any peptide for which an antibody is available can act as binding moiety-ligand pair for the purposes of isolating the peptide from a mixture. For instance, epitope tags, such as myc, can be attached to a dissimilar molecule to provide a basis for isolating the molecule. However, as the Examiner is well aware, not all peptide sequences are immunogenic, even when the peptide is linked to an immunogenic carrier. Thus, not all peptides can function as a rescue sequence if antibodies are the basis for isolating the enzyme, scaffold, or enzyme complex. Similarly, only specific peptide sequences can bind metal to function as an metal affinity tag (e.g., His_6

tag). In regards to nucleic acid sequences that can be used as a rescue sequence, it is a well known that most nucleotide sequences, synthetic or natural, is amenable to PCR amplification, which allows rescue of that sequence from even the most complex of mixtures, such as genomic DNA. A skilled artisan will understand that a sequence which cannot be used to "purify or isolate scaffolds, enzymes, or enzyme complexes, or nucleic acids encoding them" are not encompassed by the term.

In view of the foregoing, Applicants respectfully direct the Examiner to M.P.E.P. § 2173.04 which states

> Breath of a claim is not to be equated with indefiniteness. . . . If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph.

Applicants further direct the Examiner to M.P.E.P. § 2173.05(a) which recites

> [t]he requirement for clarity and precision must be balanced with the limitations of the language and the science. If the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is precise as the subject matter permits, the statute (35 U.S.C. 112, second paragraph) demands no more.

Measured against the enumerated standards, the specification has delineated the scope of "rescue sequence" with the requisite clarity and precision required by the law. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 66 for indefiniteness.

Claim 67 is rejected for being indefinite in regards to the term "stability sequence." The Examiner finds the scope of "stability sequence" is not sufficiently defined. Applicants respectfully traverse.

The specification expressly defines "stability sequence" as one which "confer stability to the expression products or the nucleic acids encoding them." The plain meaning of "stability sequence" is apparent to those skilled in the art. A sequence that does not limit loss or degradation of the expression products or nucleic acids encoding them are not stability sequences. Thus, Applicants have clearly delineated what is and what is not a stability sequence for a person skilled in the art to understand the scope of what is intended. Applicants have defined the term with the requisite degree of clarity and precision given the limitations of the language and the science. Accordingly, withdrawal of the rejection is

respectfully requested.

Rejections Under 35 U.S.C. § 102(e)

Claims 58, 59-62, 64-66, 68, 69, 72, 77 and 78 stand rejected under 35 U.S.C. § 102(e) as anticipated by Khosla et al., U.S. Pat. No. 5,672,491 (Khosla). Applicants respectfully traverse.

Khosla discloses introducing into cells gene clusters encoding multifunctional enzymes involved in polyketide synthesis. In contrast, claim 58 recites introducing a library of nucleic acids encoding enzymes comprising exogenous binding sequences. Khosla does not teach or suggest introducing nucleic acids encoding enzymes comprising exogenous binding sequences. Since Khosla fails to teach or suggest each and every limitations of the claim, Khosla fails to anticipate claim 58. Since claims 59-62, 64-66, 68, 69, 72, 77 and 78 ultimately depend in part from claim 58, these claims are not anticipated for at least the same reasons. Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 102(e) over Khosla.

Claims 58, 59, 63-70, and 74-79 stand rejected as being anticipated by Minshull et al., U.S. Patent No 5,837,458 (Minshull) with Srere, P.A., Ann. Rev. Biochem. 56: 89-91 (1987) (Srere) and Pikus et al., Biochemistry 35: 9106-9119 (1996) (Pikus) cited as extrinsic references supporting the inherency of scaffolds. Applicants respectfully traverse.

As an initial issue, Applicants address Examiner's use of inherency for a rejection under anticipation. Applicants respectfully draw the Examiner's attention to M.P.E.P. § 2112:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish inherency of that result or characteristic. . . . Inherency [] cannot be established by probabilities or possibilities. There mere fact that a certain thing may result from a given set of circumstances is not sufficient.

Minshull is directed to use of recursive sequence recombination, also termed DNA shuffling, to evolve genes with novel properties. Generally, the method relies on generating random fragments of DNAs and recombining them to produce variants that diverge from the original sequence. The product of the shuffled sequences must be screened to find those expressing the desired properties. The Examiner's recitation of the statement from Minshull illustrates this point:

> This recombination of subunits from the two dioxygenases *could* also have have been produced by cassette-shuffling of the dioxygenases as described above, followed by selection for degradation of trichorethylene.

(emphasis added). Because recombination is random and the resulting mixture must be screened, it does not necessarily flow that a DNA product encoding a set of identifying characteristics will necessarily be found by practice of the described method. An inherency rejection based on a method that is an invitation to experiment is inconsistent with the standards enumerated for anticipation by inherency.

As for the basis of rejection under § 102(e), Minshull describes introducing shuffled genes and gene clusters into cells and screening the expressed gene products for differing enzymatic properties. Minshull, as supported by Srene and Pikus does not teach or suggest introducing a library of nucleic acids encoding enzymes comprising exogenous binding sequences. Consequently Minshull does not anticipate claim 58. Since claims 59, 63-70, and 74-79 ultimately depend in part from claim 58, these claims are not anticipated for at least the same reasons. Accordingly, withdrawal of the rejections under 35 U.S.C. § 102(e) over Minshull is respectfully requested.

Rejections Under 35 U.S.C § 103(a)

Claims 71, 73, and 80 stand rejected under 35 U.S.C. § 103(a) as being rendered obvious over Minshull et al. (U.S. Pat. No. 5,837,458). Applicants respectfully traverse.

Minshull describes use of various bacterial viruses, such as filamentous bacteriophage (e.g., M13, F1, fd, phagemids), T-phage, and lamda phage to promote recombination in a bacterial cell to generate nucleic acid variants. These recombination products are then screened for a desired activity.

The M.P.E.P at § 2142 provides, in part, that to establish a *prima facie* case of obviousness, the prior art references, either alone or in combination, must teach or suggest each and every element of the rejected claims. The teaching or suggestion must come from the prior art, not applicants' disclosure. See id.; see also In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Examiner contends that Minshull suggests use of retroviral vectors. All the viruses described by Minshull, however, are bacterial viruses, which have dissimilar biochemistry, host preferences, and biological properties as compared to retroviruses. Thus, a

reference to viruses where all viruses mentioned are bacterial viruses provides no teaching or suggestion for use of retroviruses for expressing at least a first enzyme and a second enzyme as recited in the claims.

Although the Examiner states that use of retroviruses to deliver a nucleic acid encoding at least a first enzyme and a second enzyme into a cell are within the common knowledge of those skilled in the art, no such reference is provided to support this assertion. Applicants respectfully request citation of such references or an Examiner's affidavit containing the particulars of the asserted references as provided for under 37 C.F.R. § 1.104(d)(2).

Given the above, Applicants submit that Minshull fails to teach or suggest each and every element of claims 71, 73, and 80 to render these claims obvious. Accordingly, withdrawal of the rejection of claims 71, 73, and 80 under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

Applicants submit that all pending claims of the instant application are in compliance with all the requirements of patentability and are in condition for allowance. Accordingly, early notification of such allowance is earnestly solicited.

If after review, the Examiner feels there are further unresolved issues or determines that prosecution of the above reference application would benefit from a telephone interview, the Examiner is invited to call the undersigned attorney at (415) 781-1989.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

58. (Amended) A method of screening a plurality of cells, comprising:

a) producing a plurality of cells comprising a library of nucleic acids encoding a library of exogenous scaffolds;

b) introducing into said plurality of cells a library of nucleic acids each encoding at least a first enzyme and a second enzyme, wherein each of said enzymes comprises exogenous binding sequence; and

c) screening said plurality of cells for a cell comprising at least one exogenous scaffold and exhibiting an altered phenotype,

wherein each of said scaffolds comprises at least a first binding site and a second binding site, and wherein said first enzyme binds to said first binding site and said second enzyme binds to said second binding site.

APPENDIX OF PENDING CLAIMS

58. (Amended) A method of screening a plurality of cells, comprising:

a) producing a plurality of cells comprising a library of nucleic acids encoding a library of exogenous scaffolds;

b) introducing into said plurality of cells a library of nucleic acids each encoding at least a first enzyme and a second enzyme, wherein each of said enzymes comprises exogenous binding sequence; and

c) screening said plurality of cells for a cell comprising at least one exogenous scaffold and exhibiting an altered phenotype,

wherein each of said scaffolds comprises at least a first binding site and a second binding site, and wherein said first enzyme binds to said first binding site and said second enzyme binds to said second binding site.

59. (Twice Amended) The method of claim 58 or 80, further comprising contacting said cells, prior to said screening, with a library of exogenous bioactive agent precursors.

60. (Amended) A method according to claim 58 or 80, wherein each said scaffold comprises at least three binding sites.

61. (Amended) A method according to claim 58 or 80, wherein each said scaffold comprises at least four binding sites.

62. (Amended) A method according to claim 58 or 80, wherein each said scaffold comprises at least five binding sites.

63. (Amended) A method according to claim 58 or 80, wherein said cells are mammalian cells.

64. (Amended) A method according to claim 58 or 80, wherein said scaffolds are linear.

65. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids

encoding a library of exogenous scaffolds further comprises at least one targeting sequence.

66. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding a library of exogenous scaffolds further comprises at least one rescue sequence.

67. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding a library of exogenous scaffolds further comprises at least one stability sequence.

68. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding at least a first enzyme and a second enzyme further comprises at least one targeting sequence.

69. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding at least a first enzyme and a second enzyme further comprises at least one rescue sequence.

70. (Amended) A method according to claim 58 or 80, wherein said library of nucleic acids encoding at least a first enzyme and a second enzyme further comprises at least one stability sequence.

71. (Amended) A method according to claim 58 or 80, wherein said introducing comprises retroviral infection.

72. (Amended) A method according to claim 58 or 80, wherein said method further comprises isolating said cell exhibiting an altered phenotype.

73. (Amended) A method according to claim 58 or 80 further comprising isolating said scaffold from said cell exhibiting an altered phenotype.

74. (Amended) A method according to claim 58 or 80 further comprising isolating said nucleic acid encoding said scaffold from said cell exhibiting an altered phenotype.

75. (Amended) A method according to claim 58 or 80 further comprising isolating said enzymes from said cell exhibiting an altered phenotype.

76. (Amended) A method according to claim 58 or 80 further comprising isolating said nucleic acids encoding said enzymes from said cell exhibiting an altered phenotype.

77. (Amended) A method according to claim 59, wherein said altered phenotype is due to the presence of one or more of said bioactive agent precursors.

78. (Amended) A method according to claim 77 further comprising identifying said one or more bioactive agents.

79. (Amended) A method according to claim 58 or 80, wherein said nucleic acids contain localization signals.

80. A method of screening a plurality of cells, comprising:

a) producing a plurality of cells comprising a library of nucleic acids encoding a library of exogenous scaffolds;

b) introducing into said plurality of cells a library of retroviral vectors comprising nucleic acids each encoding at least a first enzyme and a second enzyme; and

c) screening said plurality of cells for a cell comprising at least one exogenous scaffold and exhibiting an altered phenotype,

wherein each of said scaffolds comprises at least a first binding site and a second binding site, and wherein said first enzyme binds to said first binding site and said second enzyme binds to said second binding site.